Exhibit 1

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CELGENE CORPORATION,	.	
	.	
Plaintiff,	.	
	.	Case No. 17-cv-03387
vs.	.	
	.	Newark, New Jersey
HETERO LABS LIMITED, et al.,	.	May 11, 2018
	.	
Defendants.	.	
	.	

TRANSCRIPT OF HEARING
BEFORE THE HONORABLE MICHAEL A. HAMMER
UNITED STATES MAGISTRATE JUDGE

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(Commencement of proceedings at 10:09 A.M.)

THE COURT: All right. So we are on the record in matter of Celgene Corporation versus Hetero Labs Limited and Celgene Corporation versus Par Pharmaceutical. The Hetero Labs Limited matter is Civil No. 17-3387. The Par Pharmaceutical matter is 17-3159.

And let me take appearances of counsel, please, beginning with Celgene.

MR. BATON: Good morning, Your Honor, Bill Baton of Saul Ewing Arnstein & Lehr, New Jersey counsel for Celgene.

MR. CERRITO: Good morning, Your Honor. Nick Cerrito and Frank Calvosa, Quinn Emanuel Urquhart & Sullivan, on behalf of Celgene.

MR. HERTKO: Good morning, Your Honor, Matt Hertko from Jones Day also on behalf of Celgene.

THE COURT: All right. Did we miss somebody? No? Okay.

Ms. Flax, how are you?

MR. FLAX: Good morning, Your Honor, Melissa Flax from Carella Byrne on behalf of Apotex and Hetero. And I'll let my cocounsel introduce themselves.

MR. ALUL: Good morning, Your Honor, Andrew Alul from Taft Stettinius & Hollister in Chicago on behalf of the Apotex and Hetero defendants.

THE COURT: All right. Good morning.

MR. FETTWEIS: Good morning, Your Honor. Robert J. Fettweis, Fleming Ruvoldt, local counsel for Breckenridge Pharmaceuticals. I'm joined by Kyle Musgrove, patent counsel, Haynes and Boone in Washington.

THE COURT: All right. Good to see you, Mr. Fettweis.

Mr. Calmann.

MR. CALMANN: Good morning, Your Honor. Arnold Calmann for Mylan. And with me is my cocounsel Ellie Steiner from Wilson Sonsini in California.

THE COURT: Ms. Steiner, how are you?

MR. CALMANN: Thank you, Your Honor.

MS. OFOSU-ANTWI: Good morning, Your Honor. Eleonore Ofosu-Antwi from the Walsh firm. And with me is my cocounsel Chris Jagoe from Kirkland & Ellis for Teva.

THE COURT: Good to see you again, counsel.

MR. WALIA: Good morning, Your Honor. This is Gurpreet Walia. And with me is cocounsel Joe Schramm for -- from FisherBroyles for Aurobindo --

THE COURT: All right. Good morning. All right. So what I'm looking at the most -- I think the most currently substantive correspondence that I have -- and if I'm wrong, please tell me -- is the Docket Entry 164. This is the Celgene Hetero Labs Limited, April 27th letter. If I recall,

you folks had proposed and I had agreed in both matters to extend the deadline to serve invalidity contentions.

MR. CERRITO: Your Honor, I think they said --

THE COURT: Go ahead.

MR. CERRITO: The April 27th letter dealt with only one particular --

THE COURT: Right. That was just Hetero. I'm looking at the March 28th letter and then the April 27th letter. The March 28th letter was both Par and Hetero. The April 27th letter, Docket Entry 164, is just Hetero.

MR. CERRITO: Right. And it dealt -- it only dealt -- it wasn't -- the 164 deals only with a schedule pertaining to Mylan.

THE COURT: Right.

MR. CERRITO: With regard to certain discovery dates there.

THE COURT: Right. So why don't we do it this way. Why don't I start with Celgene and why don't you bring me up to speed on where we are in both matters where they -- because I don't think I've had a conference in this case previously. Right? Okay.

So why don't you bring me up to speed on where we are with both matters, where they are on the same track, where they diverge, and help me just sort of generally get my bearings.

MR. CERRITO: To answer that, I guess the last question first, they're basically on the same track with the minor exception of the Mylan venue-related discovery. As Your Honor knows that's a sort of running -- a separate isolated issue with Mylan only.

Just to get Your Honor up to speed a little bit, the case was filed back in 2017. Initial disclosures in this case were exchanged in October. There are --

THE COURT: I'm sorry. You say "this case." We're on -- you're talking about both cases?

MR. CERRITO: Yeah, they were done simultaneously.

THE COURT: That's fine. Okay. So -- so go ahead.

MR. CERRITO: Everything runs together, I guess, Your Honor, essentially.

THE COURT: Okay.

MR. CERRITO: There's currently six defendants. There are seven filed, but one defendant decided to go a different route. But there are six active defendants. The number of patents asserted here are between four and nine depending on who certified as to what. So two parties have four. The remainder of the other four parties have nine patents.

The responsive contentions were exchanged back in April 20th -- not an insubstantial endeavor on behalf of, certainly, Celgene. Nearly a thousand pages were submitted

there.

As a result, now that, you know, the issues have been framed with contentions, we are now undertaking some discovery. There has been some letters back and forth between parties concerning certain of the discovery. We think that there is one issue that is ripe for a decision at this point. Of course, we'd have to file a motion or ask Your Honor for leave to file a motion. We're deciding how to approach that, so we may be --

THE COURT: Okay.

MR. CERRITO: -- approaching Your Honor in the near future. It's a sort of isolated issue.

THE COURT: With respect to both cases or just one or the other?

MR. CERRITO: I -- it'd be both.

THE COURT: Okay.

MR. CERRITO: Yes, Your Honor. I apologize. I will -- unless I guess I say --

THE COURT: Unless to the contrary.

MR. CERRITO: I just don't think of them as separate cases, so I apologize.

THE COURT: That's fine. And I still don't know what I think of them, so.... So let's try and figure all that out.

MR. CERRITO: Fair enough. Fair enough. So

we're -- again some letters have been exchanged, but it doesn't really be ripe on those issues.

We did receive some correspondence late last night concerning defendants' desire to set some dates into the schedule. We received that last night about 9 o'clock. We have not, obviously, had a chance to discuss that with our client.

We're happy to discuss that with defendants and get back to Your Honor with a recommendation or hopefully an agreement.

THE COURT: Yeah, you actually presage my next question, which is I know that there were -- well, actually I don't know. Whether we're operating under a viable pretrial scheduling order at this point.

MR. CERRITO: Your Honor, I guess I don't presume to understand what you mean by one --

THE COURT: In other words. Go ahead.

MR. ALUL: I was just going to say, Your Honor, I don't believe we are. We're operating on a truncated schedule at best that basically leaves a number of dates open after -- after the claim construction schedule. And we're almost a year into this case -- I believe we're 10 months into this case. We're eight months into fact discovery. I generally agree with what Mr. Cerrito's synopsis of what's happened in this case, except that I believe we've engaged in

some very considerable fact discovery. We served our Rule 34 requests, Rule 33 interrogatories. We've gotten responses back from them. We're working through some deficiencies with them. We've served our invalidity contentions, our noninfringement contentions. Hundreds of pages. They served their response and their infringement contentions.

THE COURT: Right.

MR. ALUL: Both sides have exchanged hundreds, if not thousands, of pages of prior art and other documentary evidence in connection with those contentions. Really, the only thing we have left to do is take fact deps. And I believe Celgene has yet to serve Rule 34 requests for documents. They've already served Rule 34 requests for samples. We've produced those.

So we've had significant fact discovery underway here. And at least on the defense side, we believe we need a schedule.

MR. CERRITO: Well, Your Honor, I -- had most of it, right up until part where he said --

THE COURT: No, I didn't hear a lot of disagreement. But, right.

MR. CERRITO: Well -- said we're basically done. I mean, we basic just started is where we are.

Once contentions are served to the parties --

THE COURT: This is going to get interesting.

Okay.

MR. CERRITO: I mean, that's when you know what your case is. Right? They served their contentions. We responded. They did hundreds. We did thousands in response.

And now we know where -- that happened April 20th, so couple of weeks ago, basically, we framed the case.

Look, we have no problem talking about a schedule. We'll do that offline and present to Your Honor.

THE COURT: Yeah.

MR. CERRITO: Unfortunately, we were sort of sandbagged by their attempt to rush into court with a schedule that never raising it --

THE COURT: I'm sure no sandbagging was intended.

But, look, why don't we do it this way, right, and approach it practically. How about if I give you folks two weeks -- and if this isn't enough time because we have -- we have multiple parties, tell me. I'll be happy to work with you -- to meet and confer and try to get me a schedule. And actually, shame on me, I probably should have done that in the run-up to this conference. But no harm, no foul.

So if two weeks is enough time.

And then if you folks, as you most certainly will, disagree on this part or that part of the schedule, you'll tell me in that submission what your respective disagreement is, and each of you can please concisely tell me the basis

for your position as to that aspect of the schedule on which you disagree.

MR. CERRITO: Yes, Your Honor.

MR. ALUL: Happy to do that, Your Honor.

I'd just like to push back on this assertion somehow we sandbagged them. We asked them on Monday actually for -- then I'll leave it alone.

THE COURT: You're arguing when you're ahead.

MR. ALUL: I'm sorry?

THE COURT: You're arguing while you're ahead. No, I didn't infer sandbagging.

MR. ALUL: Thank you. But we have a proposed schedule here with us, but we're happy to meet and confer with them. Yeah.

THE COURT: Yes, please do that. Look, if nothing else, I don't expect you folks -- just experience teaches me that you won't agree on the entirety of the schedule, especially if there's at least some disagreement over what's been accomplished, but at least in doing this -- look, here's the truth about being a magistrate judge in complex civil litigation. Okay? Unless you're Stanley Chesler, who's obviously no longer a magistrate judge and hasn't been in a while. But half the time, you're just trying to figure out where the disagreement lies. Okay? And you're doing it in, you know, with 10 other conferences going on that day, a

settlement conference that may or may not actually settle. You don't know because you're only in hour 3, and you still don't know exactly where the parties are.

So the best thing can you do by meeting and conferring, if you -- look, in a perfect world, you'll agree on everything. But in a less than perfect world, at least you'll tell me where you disagree and why, and that'll let me get through it a lot more quickly and get you folks back an order that reconciles the issues.

MR. ALUL: Thank Your Honor.

THE COURT: All right. What else you got?

MR. CERRITO: Nothing, Your Honor.

THE COURT: Okay.

DEFENSE ATTORNEY: Your Honor, the only question I have is I know that this is unusual in New Jersey, but given the 30-month stay date, would it be possible to talk to Judge Salas about getting a trial date. That we had originally proposed that back in front of Judge -- the other magistrate judge in January.

THE COURT: And I'm going to guess, did he say in a sort of skeptical tone, you can ask?

DEFENSE ATTORNEY: I think we actually -- my record of -- is that he said he would talk to her. In fact, Your Honor, if you look -- my recollection at that time was that he said he would check with Judge Salas, but, obviously,

if we had a trial date, then it's much easier to work backwards. If that's certainly not something that's done here, we're fine with that. But --

THE COURT: I can -- maybe I'm betraying just sheer ignorance. I've not heard of that practice before.

Mr. Cerrito, do you want to --

MR. CERRITO: I've never heard of that either, Your Honor. And just so we're on --

THE COURT: I'm not saying it doesn't happen. I'm just saying I haven't heard of that previously.

MR. CERRITO: I've had, as Your Honor knows, many cases before Judge Salas. I've never heard that.

But the 30-month stay in this case is more than two years away. This was actually a 42-month stay because of the "date certain" filing. So it's August 2020. I don't know that we can talk about trial dates two and a half years from now.

MR. ALUL: Just to clarify, Your Honor, in the Rule 16 transcript, Judge Dickson did say that he would check with Judge Salas.

THE COURT: I'm not doubting.

MR. ALUL: Yeah.

THE COURT: Yeah, I don't doubt that.

MR. ALUL: But we're certainly willing to follow whatever the Court's predilection is on this.

THE COURT: Here's what I propose you do. Hold on. Let me see if I can find it in the transcript. I was going to suggest first submitting a letter, but if it's already in the transcript, I'm not sure that that's entirely necessary.

MR. ALUL: Yes, it's -- Your Honor. We have some citations. It's actually in the scheduling order that's in place. It's Footnote 2 in the calendar attached to the schedule. And you'll see hearing transcript, October 25th, 2017, at 14:24 to 16:5, and then 49 --

THE COURT: I'm sorry. Wait. Hold on. Let me just catch up with you.

MR. ALUL: Sure.

THE COURT: October -- tell me that again. What's the date?

MR. ALUL: Sure. It's October 25th, 2017, is the transcript of the Rule 16.

THE COURT OFFICER: What page?

MR. ALUL: Page 14 to 16, and page 49, lines 4 through 19. I actually have it on my phone. I don't have a hard copy of it here with me.

THE COURT: It's all right. I've got it here -- or I will.

MR. CERRITO: What may be missing from that written word is the skepticism Judge Dickson showed when that statement was made.

But regardless, Your Honor, we're talking about a case --

THE COURT: I'll raise the issue. I mean --

MR. CERRITO: I would encourage you to talk to Judge Dickson.

THE COURT: J, did you make a note of those page -- what are the pages again? I'm sorry.

MR. ALUL: Sure. They 14 to 16 and 49.

THE COURT: Okay. All right.

MR. CERRITO: I think it's, quite frankly, a little unproductive to do this piecemeal and present to Your Honor a full picture.

THE COURT: Here's the other problem -- right? -- realistically with predicting a trial schedule or a trial date two years out. As you folks know, and certainly Judge Salas is eminently sensitive to the 30-month stay issue. But we also operate -- or she operates as a district judge in a world where criminal cases get priority constitutionally, and trying to predict exactly an open date, you know, in a case for trial purposes is at this point extraordinarily difficult and speculative.

But I'll take a look at the transcript, and I'll talk about it.

MR. CERRITO: I guess I would just add, if we're going to go down this road, you know, obviously, this Court's

well aware of Local Rule 2.4 about Markman scheduling and what expert reports follow therefrom. We obviously agree with the rule. We think that you should have Markman ruling before you end up doing expert reports, and maybe more so in this case than in others, since there are so many defendants.

THE COURT: Right.

MR. CERRITO: There's going to be -- and I'm guessing, between all the parties -- remember, I have to show infringement against all of them. I mean, the different experts against all of them. There could easily be 15 to 20 experts in this case. To rush with the schedule, to work backwards to set a date when we don't have a Markman may require us to do two sets of expert reports, may require amended contentions, may require all the things that Rule 2.4 was set up to avoid.

THE COURT: Right. I'll say this outset, I'd have some real concerns about locking in a schedule now, just getting sort of up to speed on the case.

MR. ALUL: Understood, Your Honor. I -- again, we just --

THE COURT: I understand the idea and the purpose behind it.

MR. ALUL: We didn't -- the issue for us is, Your Honor, we're in this case. We've been in this case now for almost a year or eight months in the fact discovery.

THE COURT: Right.

MR. ALUL: We've hired experts who -- some of whom are physicians, some of whom are university professors who have very busy schedules who are calling me every month saying, when are our services going to be needed?

We have corporate clients who for budgetary reasons need to know when big litigation expenditures are going to take place in this case.

THE COURT: Yeah, well, I have to be honest, on that one, your corporate clients are use -- especially in these sort of cases, this is probably something that they've grown accustomed or adapted to by now.

MR. ALUL: Understood. Okay. Fair enough, Your Honor.

I guess my point is, though, we've been in this case for a year and a half now. We've hired experts -- for -- I'm sorry -- for a year now. We're eight months into fact discovery. We know --

THE COURT: He was about to get up and object to year and a half.

(Simultaneous conversation)

THE COURT: And you even see him out of the corner of your eyes, so I would think --

(Simultaneous conversation)

MR. CERRITO: See, I don't even have to say

anything. I just have to look like I'm going to stand up.

MR. ALUL: So, you know, again, I find it -- I've practiced before this Court for years now, and I find it unusual that we're almost a year into this case, and we don't have a complete schedule; set aside the trial date issue. And I think we, on the defense side, would find it very helpful if we could lock in some days.

THE COURT: Well, look, at a minimum, here's what I can promise you. By the end of -- you folks are going to get me the joint letter by when? We said in two weeks. Right?

MR. ALUL: Sure.

THE COURT: So that's the 25th. By the end of the month, we're going to have a schedule.

MR. ALUL: Great. Thank you, Your Honor.

THE COURT: It may not have a trial date on it.

MR. ALUL: Sure.

THE COURT: But we're going to have a schedule.

MR. ALUL: Understood.

THE COURT: What else? Nothing?

MR. ALUL: Your Honor, there was one last issue that we were going to bring up for Apotex and Hetero, and we'd be happy to submit a formal letter application on this particular issue, if Your Honor would like.

THE COURT: Okay.

MR. ALUL: There are, as Mr. Cerrito mentioned,

nine patents in this case for, I guess, four of the defendant, including both of my clients. One of the patents is a formulation patent. It's a very specific formulation patent. It claims specific capsules of pomalidomide with certain ingredients and certain amounts, weighing certain amounts and having certain sizes. It's a very, very narrow patent. And my clients have designed around it. And we don't infringe. In fact, a few weeks ago, we got Celgene's infringement contentions, which we're still digesting, but they actually concede no literal infringement. They only assert infringement under the doctrine of equivalents. And there, Your Honor, the case law's pretty crystal-clear, Celgene's estopped from asserting infringement of the doctrine of equivalents for two independent reasons: because of how they narrowed their claims during claim construction to avoid the prior art, and because of what they told the Patent Office about their claims to distinguish them from the prior art. And under Federal Circuit case law, Your Honor, prosecution history estoppel is a legal issue for the Court to decide via pretrial summary judgment motion. So --

THE COURT: Okay. So -- I'm sorry -- wait. So tell me what the request is.

MR. ALUL: So the request is -- the request is for leave to file for summary judgment on this one patent. And we'd be happy to present it as a letter application to

Your Honor.

THE COURT: Yeah, you're probably going to need to, because that's going to be much more Judge Salas's call than mine, but go ahead, Mr. Cerrito.

MR. ALUL: Sure.

MR. CERRITO: I mean, besides disagreeing with everything he just said, and there is a legal issue --

THE COURT: I imagine on the law, you did. But --

MR. CERRITO: Yeah, and I do -- and also it's an issue underlying --

THE COURT: Do you concede that there's no literal infringement, though?

MR. CERRITO: I believe that is what we said in our -- in the papers.

THE COURT: Okay. Okay.

MR. CERRITO: But the underlying question of law there, of course, is based on facts. And so, again -- I know he's been here a long time, I've been here a long time, we've all been here a long time, and rarely do we see summary judgment motions for all the reasons that judges typically don't allow them, because they waste time. On the one hand, they want to move forward quickly and do all this stuff, but on the other hand, they want to distract us.

THE COURT: Well, they're not proposing to stay discovery. I mean, you're not proposing to stay discovery.

MR. ALUL: Oh, no.

THE COURT: Right. That's not happening.

MR. CERRITO: But when it's six against -- when it's six against one -- easy for them to do that, because they can all do the work. I have to do the work against all of them. They can choose which one of them does the work.

So, you know, they can make their application, I guess, Your Honor, but obviously, we would -- we're going to oppose.

THE COURT: Well, I assume you're going to want to be heard on that? So you folks will send me a joint letter? Unless you don't want to be heard.

MR. ALUL: Sure.

MR. CERRITO: I mean, I want to be heard to oppose, yes.

THE COURT: Yeah, to oppose him, leave to make the motion. I assume that you're -- obviously you want to -- you want to be heard on opposing any motion, if it's allowed.

MR. CERRITO: Whatever -- yes, Your Honor.

THE COURT: All right. So what I'll do --

MR. CERRITO: Well, if a motion will be allowed.

MR. BATON: Yeah, Your Honor, it's Bill Baton. Just to be clear, I think what you're asking is he -- they want to put in a letter --

THE COURT: Yeah.

MR. BATON: -- requesting leave to file a motion.

THE COURT: And I want to know -- your side why that's a bad idea.

MR. BATON: Yes. Right.

MR. CERRITO: Yes, Your Honor.

MR. BATON: But he's just not going to file a motion.

THE COURT: No.

MR. BATON: Right. Correct.

THE COURT: All right. So why don't you folks get that to me also by the 25th.

MR. ALUL: Thank Your Honor.

THE COURT: Okay. Okay. Anything else? All right. We're adjourned.

(Conclusion of proceedings at 10:29 A.M.)

Certification

I, SARA L. KERN, Transcriptionist, do hereby certify that the 24 pages contained herein constitute a full, true, and accurate transcript from the official electronic recording of the proceedings had in the above-entitled matter; that research was performed on the spelling of proper names and utilizing the information provided, but that in many cases the spellings were educated guesses; that the transcript was prepared by me or under my direction and was done to the best of my skill and ability.

I further certify that I am in no way related to any of the parties hereto nor am I in any way interested in the outcome hereof.

S/ *Sara L. Kern* 17th of May, 2018

Signature of Approved Transcriber Date

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Exhibit 2

[redacted]

[redacted]

Exhibit 3

[redacted]

[redacted]

[redacted]

Exhibit 4

[redacted]

[redacted]

Exhibit 5

From: Frank Calvosa
Sent: Monday, July 09, 2018 4:09 PM
To: Joseph Schramm; Andrew Chalson; Pomalyst; Celgene_JD_Lit@jonesday.com; clizza@saul.com; wbaton@saul.com; Moses, David L.
Cc: Gurpreet Walia; Gary Ji
Subject: RE: Celgene v. Par, Hetero (pomalidomide): Amendments to Non-infringement Contentions
Attachments: REDLINE - Aurobindo Amended Non-infringement Contentions - 427 patent (QE Response).pdf

Counsel,

Provided that Aurobindo agrees that Celgene may amend its infringement contentions to address Aurobindo's amendments within 45 days of Aurobindo's amended non-infringement contentions being entered by the Court, Celgene agrees to Aurobindo's proposed amendments with the exception of those highlighted in the attached. Celgene is willing to meet and confer regarding its position.

Best,

Frank Calvosa
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From: Joseph Schramm [mailto:joseph.schramm@FisherBroyles.com]
Sent: Friday, June 29, 2018 8:27 PM
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Cc: Gurpreet Walia <Gurpreet.Walia@fisherbroyles.com>; Gary Ji <Gary.Ji@fisherbroyles.com>
Subject: RE: Celgene v. Par, Hetero (pomalidomide): Amendments to Non-infringement Contentions

Frank,

Attached is a redline comparing Aurobindo's proposed amended non-infringement contentions that we circulated yesterday against Aurobindo's original contentions. We propose that Aurobindo's non-infringement contentions for the other patents would remain unchanged, despite this redline showing edits in those sections because we only provided those pertinent sections of the proposed amended non-infringement contentions that relate to the '427 patent.

Regards,

Joe

Joseph Schramm, III, Esq.
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From: Frank Calvosa [mailto:frankcalvosa@quinnemanuel.com]
Sent: Friday, June 29, 2018 11:41 AM
To: Joseph Schramm <joseph.schramm@FisherBroyles.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; Pomalyst <pomalyst@quinnemanuel.com>; Celgene_JD_Lit@jonesday.com; clizza@saul.com; wbaton@saul.com; Moses, David L. <David.Moses@saul.com>
Cc: Gary Ji <Gary.Ji@fisherbroyles.com>
Subject: RE: Celgene v. Par, Hetero (pomalidomide): Amendments to Non-infringement Contentions

Counsel,

Can you please provide a redline against Aurobindo's original contentions so that we may consider.

Thanks,

Frank Calvosa
Associate
Quinn Emanuel Urquhart & Sullivan, LLP

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Cc: Gary Ji <Gary.Ji@fisherbroyles.com>
Subject: RE: Celgene v. Par, Hetero (pomalidomide): Amendments to Non-infringement Contentions

Counsel,

Attached are Aurobindo's and Eugia's proposed amendments to their non-infringement contentions. For purposes of Celgene considering whether to consent to this request, we've included only those portions of the non-infringement contentions relating to the '427 patent because those are the only sections of the non-infringement contentions to which Aurobindo and Eugia propose amendments at this time.

Please let us know by July 6, 2018 whether Celgene will consent to this amendment.

Exhibit 6

From: Scharn, Nathan [mailto:nscharn@wsgr.com]
Sent: Monday, July 23, 2018 4:44 PM
To: Frank Calvosa <frankcalvosa@quinnemanuel.com>; Hanson, Tina <thanson@wsgr.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; Pomalyst <pomalyst@quinnemanuel.com>; Moses, David L. <David.Moses@saul.com>; Matthew J Hertko <mhertko@jonesday.com>; Cary Miller <cmiller@jonesday.com>; Clark, Douglas L. <dlclark@jonesday.com>; Anthony Insogna <aminsogna@jonesday.com>; Steven J Corr <sjcorr@JonesDay.com>; Celgene_JD_Lit@jonesday.com; Slavin, Elina <Elina.Slavin@saul.com>; *wbaton@saul.com <wbaton@saul.com>; DuFault, Andrea L. <aldufault@JonesDay.com>; *clizza@saul.com <clizza@saul.com>
Cc: Kong, T.O. <TKong@wsgr.com>; Steiner, Ellie <esteiner@wsgr.com>; Siedlak, Sarah <ssiedlak@wsgr.com>; Arnie Calmann <ACalmann@saiber.com>; Jakob B. Halpern <JHalpern@saiber.com>
Subject: RE: Celgene v. Par, Hetero Non-infringement Contentions

Counsel,

Thank you for taking the time to meet and confer last week. As discussed on the call, the parties are at an impasse with respect to the Mylan Defendants' proposed amended non-infringement contentions, and the Mylan Defendants will seek relief with the Court.

Regards,
Nathan

Nathaniel R. Scharn ▪ Wilson Sonsini Goodrich & Rosati, PC
12235 El Camino Real, Suite 200, San Diego, CA 92130-3002
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From: Frank Calvosa [mailto:frankcalvosa@quinnemanuel.com]
Sent: Thursday, July 19, 2018 7:39 AM
To: Scharn, Nathan; Hanson, Tina; Andrew Chalson; Pomalyst; Moses, David L.; Matthew J Hertko; Cary Miller; Clark, Douglas L.; Anthony Insogna; Steven J Corr; Celgene_JD_Lit@jonesday.com; Slavin, Elina; *wbaton@saul.com; DuFault, Andrea L.; *clizza@saul.com
Cc: Kong, T.O.; Steiner, Ellie; Siedlak, Sarah
Subject: RE: Celgene v. Par, Hetero Non-infringement Contentions

Nathan,

We can be available Friday at 11 am PT/2 pm ET. Please circulate a dial in.

Thank you,

Frank Calvosa
Associate
Quinn Emanuel Urquhart & Sullivan, LLP

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From: Scharn, Nathan [mailto:nscharn@wsgr.com]
Sent: Wednesday, July 18, 2018 5:53 PM
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Cc: Kong, T.O. <TKong@wsgr.com>; Steiner, Ellie <esteiner@wsgr.com>; Siedlak, Sarah <ssiedlak@wsgr.com>
Subject: RE: Celgene v. Par, Hetero Non-infringement Contentions

Frank,

Please provide your availability for Thursday between 3 PM and 5 PM PT and Friday between 9:30 AM and 3 PM PT to meet and confer regarding Celgene's objection.

Regards,
Nathan

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Cc: Kong, T.O.; Steiner, Ellie; Scharn, Nathan; Siedlak, Sarah
Subject: RE: Celgene v. Par, Hetero Non-infringement Contentions

Counsel,

Celgene objects to Mylan's proposed amended non-infringement contentions. Celgene is willing to meet and confer regarding its position.

Best,

Frank Calvosa
Associate
Quinn Emanuel Urquhart & Sullivan, LLP

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Cc: Kong, T.O. <TKong@wsgr.com>; Steiner, Ellie <esteiner@wsgr.com>; Scharn, Nathan <nscharn@wsgr.com>; Siedlak, Sarah <ssiedlak@wsgr.com>
Subject: Celgene v. Par, Hetero Non-infringement Contentions

Counsel,

Further to the correspondence between the parties, attached is a draft of the Mylan Defendants' proposed supplemental non-infringement contentions. Please let us know if Celgene consents to our application to serve these contentions.

Regards,
Tina

Tina Hanson
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Exhibit 7

Exhibit 8

US008828427B2

(12) **United States Patent**
Tutino et al.

(10) **Patent No.: US 8,828,427 B2**
(45) **Date of Patent: Sep. 9, 2014**

(54) **FORMULATIONS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE**

(75) Inventors: **Anthony Tutino**, New Providence, NJ (US); **Michael T. Kelly**, Lake Hopatcong, OH (US)

(73) Assignee: **Celgene Corporation**, Summit, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 398 days.

(21) Appl. No.: **12/783,390**

(22) Filed: **May 19, 2010**

(65) **Prior Publication Data**

US 2011/0045064 A1 Feb. 24, 2011

Related U.S. Application Data

(60) Provisional application No. 61/179,678, filed on May 19, 2009.

(51) **Int. Cl.**
A61K 31/454 (2006.01)
A61K 9/48 (2006.01)

(52) **U.S. Cl.**
USPC **424/452**; 514/323

(58) **Field of Classification Search**
CPC A61K 31/454; A61K 47/26; A61K 47/36; A61K 9/4858; A61K 9/4866
USPC 424/452; 514/323
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,593,696 A * 1/1997 McNally et al. 424/472
2007/0155791 A1 * 7/2007 Zeldis et al. 514/323

FOREIGN PATENT DOCUMENTS

WO WO 2006/058008 A1 6/2006

OTHER PUBLICATIONS

Remington's Pharmaceutical Sciences 17th Edition, Published 1985, pp. 1613-1615 and 1625-1626.*
Crane and List, "Immunomodulatory Drugs," Cancer Investigation 23(7): 625-634 (2005).

* cited by examiner

Primary Examiner — Richard Schnizer
Assistant Examiner — Alma Pipic
(74) *Attorney, Agent, or Firm* — Jones Day

(57) **ABSTRACT**

Pharmaceutical compositions and single unit dosage forms of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate, are provided herein. Also provided are methods of treating, managing, or preventing various disorders, such as cancer or an inflammatory disease.

12 Claims, No Drawings

FORMULATIONS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE

This application claims priority to U.S. Provisional Application No. 61/179,678, filed May 19, 2009, the entirety of which is incorporated herein by reference.

1. FIELD

Provided herein are formulations and dosage forms of pomalidomide, i.e., 4-amino-2-(2,6-dioxopiperidine-3-yl) isoindoline-1,3-dione or CC-4047. Methods of using the formulations and dosage forms are also provided herein.

2. BACKGROUND

Drug substances are usually administered as part of a formulation in combination with one or more other agents that serve varied and specialized pharmaceutical functions. Dosage forms of various types may be made through selective use of pharmaceutical excipients. As pharmaceutical excipients have various functions and contribute to the pharmaceutical formulations in many different ways, e.g., solubilization, dilution, thickening, stabilization, preservation, coloring, flavoring, etc. The properties that are commonly considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage form. Due to the varying properties of the active drug substance to be formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored to the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

Pomalidomide, which is also known as CC-4047, is chemically named 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is an immunomodulatory compound that inhibits, for example, LPS induced monocyte TNFα, IL-1β, IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production. The compound is also known to co-stimulate the activation of T-cells. Pomalidomide and method of synthesizing the compound are described, e.g., in U.S. Pat. No. 5,635,517, the entirety of which is incorporated herein by reference.

Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders. Thus, a need exists as to dosage forms of pomalidomide having advantageous physical and pharmaceutical properties.

3. SUMMARY

Provided herein are pharmaceutical dosage forms of pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof. Also provided herein are methods of treating, managing, or preventing diseases and conditions such as, but not limited to, cancer, pain, Macular Degeneration, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis, a sleep disorder, hemoglobinopathy, anemia, an inflammatory disease, an autoimmune disease, a viral disease, a genetic disease, an allergic disease, a bacterial disease, an ocular neovascular disease, a choroidal neovascular disease, a retina neovascular disease, and rubeosis, using pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof, in the dosage forms described herein.

3.1. Definitions

As used herein and unless otherwise indicated, a composition that is "substantially free" of a compound means that the composition contains less than about 20 percent by weight, more preferably less than about 10 percent by weight, even more preferably less than about 5 percent by weight, and most preferably less than about 3 percent by weight of the compound.

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80 percent by weight of one stereoisomer of the compound and less than about 20 percent by weight of other stereoisomers of the compound, more preferably greater than about 90 percent by weight of one stereoisomer of the compound and less than about 10 percent by weight of the other stereoisomers of the compound, even more preferably greater than about 95 percent by weight of one stereoisomer of the compound and less than about 5 percent by weight of the other stereoisomers of the compound, and most preferably greater than about 97 percent by weight of one stereoisomer of the compound and less than about 3 percent by weight of the other stereoisomers of the compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center.

As used herein, unless otherwise specified, the term "pharmaceutically acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic moieties of thalidomide. Basic moieties are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions. Suitable organic acids include, but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, acetic, formic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, oleic, tannic, aspartic, stearic, palmitic, glycolic, glutamic, gluconic, glucaronic, saccharic, isonicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, benzenesulfonic acids, or pamoic (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate) acids. Suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, or nitric acids. Compounds that include an amine moiety can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Chemical moieties that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts are alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, or iron salts.

As used herein, and unless otherwise specified, the term "solvate" means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-sto-

ichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

As used herein and unless otherwise indicated, the teen "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of thalidomide that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of thalidomide that include —NO, —NO_2, —ONO, or —ONO_2 moieties.

As used herein and unless otherwise indicated, the terms "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean a carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein and unless otherwise indicated, the term "biohydrolyzable ester" means an ester of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein and unless otherwise indicated, the term "biohydrolyzable amide" means an amide of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder, or retards or slows the progression of the disease or disorder.

As used herein, and unless otherwise specified, the terms "prevent," "preventing" and "prevention" refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. The terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder.

As used herein, and unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

As used herein, and unless otherwise specified, the term "about," when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, means dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent is encompassed. Specifically, the term "about" contemplates a dose, amount, or weight percent within 30%, 25%, 20%, 15%, 10%, or 5% of the specified dose, amount, or weight percent is encompassed.

As used herein, and unless otherwise specified, the term "stable," when used in connection with a formulation or a dosage form, means that the active ingredient of the formulation or dosage form remains solubilized for a specified amount of time and does not significantly degrade or aggregate or become otherwise modified (e.g., as determined, for example, by HPLC). In some embodiments, about 70 percent or greater, about 80 percent or greater or about 90 percent or greater of the compound remains solubilized after the specified period.

4. DETAILED DESCRIPTION

Provided herein are pharmaceutical dosage forms of pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof. In some embodiments, the dosage forms are suitable for oral administration to a patient. In other embodiments, the dosage forms provided herein exhibit advantageous physical and/or pharmacological properties. Such properties include, but are not limited to, ease of assay, content uniformity, flow properties for manufacture, dissolution and bioavailability, and stability. In certain embodiments, the dosage forms provided herein have a shelf life of at least about 12 months, at least about 24 months, or at least about 36 months without refrigeration.

Also provided herein are kits comprising pharmaceutical compositions and dosage forms provided herein. Also provided herein are methods of treating, managing, and/or preventing a disease or condition, which comprises administering to a patient in need thereof a pharmaceutical composition or a dosage form provided herein.

4.1 Compositions and Dosage Forms

In one embodiment, provided herein is a single unit dosage form suitable for oral administration to a human comprising: an amount equal to or greater than about 1, 5, 10, 15, 20, 25, 30, 50, 75, 100, 150, or 200 mg of an active ingredient; and a pharmaceutically acceptable excipient; wherein the active ingredient is pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof. In some embodiments, the amount of active ingredient is from about 0.1 to about 100 mg, from about 0.5 to about 50 mg, from, about 0.5 to about 25 mg, from about 1 mg to about 10 mg, from about 0.5 to about 5 mg, or from about 1 mg to about 5 mg. In one embodiment, the amount of the active ingredient is about 0.5 mg. In another embodiment, the amount of the active ingredient is about 1 mg. In another embodiment, the amount of the active ingredient is about 2 mg. In another embodiment, the amount of the active ingredient is about 5 mg.

Pharmaceutical compositions and formulations provided herein can be presented as discrete dosage forms, such as

capsules (e.g., gelcaps), caplets, tablets, troches, lozenges, dispersions, and suppositories each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Because of their ease of administration, tablets, caplets, and capsules represent a preferred oral dosage unit forms.

Tablets, caplets, and capsules typically contain from about 50 mg to about 500 mg of the pharmaceutical composition (i.e., active ingredient and excipient(s)). Capsules can be of any size. Examples of standard sizes include #000, #00, #0, #1, #2, #3, #4, and #5. See, e.g., *Remington's Pharmaceutical Sciences*, page 1658-1659 (Alfonso Gennaro ed., Mack Publishing Company, Easton Pa., 18th ed., 1990), which is incorporated by reference. In some embodiments, capsules provided herein are of size #1 or larger, #2 or larger, or #4 or larger.

Also provided herein are anhydrous pharmaceutical compositions and dosage forms including an active ingredient, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5 percent) is widely accepted in the pharmaceutical arts as a means of simulating shelf-life, i.e., long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate decomposition. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

An anhydrous pharmaceutical compositions should be prepared and stored such that the anhydrous nature is maintained. Accordingly, in some embodiments, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

In this regard, also provided herein is a method of preparing a solid pharmaceutical formulation including an active ingredient through admixing the active ingredient and an excipient under anhydrous or low moisture/humidity conditions, wherein the ingredients are substantially free of water. The method can further include packaging the anhydrous or non-hygroscopic solid formulation under low moisture conditions. By using such conditions, the risk of contact with water is reduced and the degradation of the active ingredient can be prevented or substantially reduced.

Also provided herein are lactose-free pharmaceutical compositions and dosage forms. Compositions and dosage forms that comprise an active ingredient that is a primary or secondary amine are preferably lactose-free. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient that is a primary or secondary amine. Lactose-free compositions provided herein can comprise excipients which are well known in the art and are listed in the USP (XXI)/NF (XVI), which is incorporated herein by reference.

In one embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises from about 0.1 to about 10 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises from about 0.1 to about 5 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises from about 0.1 to about 3 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises from about 0.5 to about 3 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises from about 0.5 to about 2 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises about 1 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises about 0.8 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises about 2 weight percent of total weight of the composition. In another embodiment, pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, comprises about 1.7 weight percent of total weight of the composition.

In one embodiment, the active ingredient and carrier, diluent, binder, or filler are directly blended as described herein elsewhere. In another embodiment, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment, the carrier, diluent, binder, or filler comprises from about 70 to about 99 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises from about 80 to about 99 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises from about 85 to about 99 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises from about 90 to about 99 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises from about 95 to about 99 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises about 98 weight percent of total weight of the composition. In another embodiment, the carrier, diluent, binder, or filler comprises about 99 weight percent of total weight of the composition.

In one embodiment, the dosage forms provided herein comprise both mannitol and starch. In one embodiment, mannitol and starch comprise from about 70 to about 99 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise from about 80 to about 99 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise from about 85 to about 99 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise from about 90 to about 99 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise from about 95 to about 99 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise about 98 weight percent of total weight of the composition. In another embodiment, mannitol and starch comprise about 99 weight percent of total weight of the composition.

In one embodiment, the ratio of mannitol:starch in the dosage form is from about 1:1 to about 1:1.5. In one embodiment, the ratio of mannitol:starch in the dosage form is about 1:1.3.

In another embodiment, the dosage form comprises a lubricant. In one embodiment, the dosage form comprises about 0.2, 0.3, 0.5, 0.6, or 0.8 mg of lubricant. In another embodiment, the dosage form comprises about 0.16, 0.32, 0.64, or 0.75 mg of lubricant. In one embodiment, the lubricant is sodium stearyl fumarate (PRUV).

In one embodiment, the lubricant, e.g., PRUV, comprises from about 0.01 to about 5 weight percent of total weight of the composition. In another embodiment, the lubricant, e.g., PRUV, comprises from about 0.01 to about 1 weight percent of total weight of the composition. In another embodiment, the lubricant, e.g., PRUV, comprises from about 0.1 to about 1 weight percent of total weight of the composition. In another embodiment, the lubricant, e.g., PRUV, comprises from about 0.1 to about 0.5 weight percent of total weight of the composition. In another embodiment, the lubricant, e.g., PRUV, comprises from about 0.2 to about 0.3 weight percent of total weight of the composition. In another embodiment, the lubricant, e.g., PRUV, comprises about 0.25 weight percent of total weight of the composition.

In some embodiments, because it is typical to obtain pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at a purity of less than 100%, the formulations and dosage forms provided herein may be defined as compositions, formulations, or dosage forms that comprise pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at an amount that provides the potency of a specified amount of 100% pure pomalidomide.

For example, in one embodiment, provided herein is a single unit dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 0.5, 1, 2, 3, 4, or 5 mg potency of pomalidomide; and 2) about 60, 120, 250, 180, 240, or 300 mg of a carrier, diluent, binder, or filler, respectively. In one embodiment, the amount of a carrier, diluent, binder, or filler is about 62, 124, 248, 177, 236, or 295 mg, respectively.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof present at an amount that provides about 0.5 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 62.5 mg. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 62.5 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 35 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 62.5 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.2 mg. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.16 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 0.5 mg potency of pomalidomide; 2) about 35 mg of pregelatinized starch; 3) about 0.16 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 62.5 mg. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 1 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 125 mg. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 125 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 70 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 125 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.3 mg. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.32 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 1 mg potency of pomalidomide; 2) about 70 mg of pregelatinized starch; 3) about 0.32 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 125 mg. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 2 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 250 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 250 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 140 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 250 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.6 mg. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.64 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 2 mg potency of pomalidomide; 2) about 140 mg of pregelatinized starch; 3) about 0.64 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 250 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 3 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 180 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 180 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 100 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 180 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.5 mg. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.45 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 3 mg potency of pomalidomide; 2) about 100.8 mg of pregelatinized starch; 3) about 0.45 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 180 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 4 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 240 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 240 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 135 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 240 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.6 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 4 mg potency of pomalidomide; 2) about 134.4 mg of pregelatinized starch; 3) about 0.6 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 240 mg. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 5 mg potency of pomalidomide; and 2) a pharmaceutically acceptable excipient. In one embodiment, the total weight of the dosage form is about 300 mg. In one embodiment, the dosage form is suitable for administration in a size 1 or larger capsule. In one embodiment, the excipient comprises a carrier, diluent, binder, or filler. In one embodiment, the excipients comprise a carrier, diluent, binder, or filler and a lubricant.

In one embodiment where the total weight of the dosage form is about 300 mg, the carrier, diluent, binder, or filler comprises mannitol and/or starch. In one embodiment, the excipient comprises both mannitol and starch. In one embodiment, where both mannitol and starch are present in the dosage form, the dosage form comprises about 168 mg of starch, and the remaining weight is filled by starch. In one embodiment, the mannitol is spray dried mannitol. In another embodiment, the starch is pregelatinized starch.

In one embodiment where the total weight of the dosage form is about 300 mg and where a lubricant is present, the lubricant is sodium stearyl fumarate. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.8 mg. In one embodiment, the sodium stearyl fumarate is present at an amount of about 0.75 mg.

In one embodiment, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 5 mg potency of pomalidomide; 2) about 168 mg of pregelatinized starch; 3) about 0.75 mg of sodium stearyl fumarate; and 4) spray dried mannitol at an amount that brings the total weight of the dosage form to 300 mg. In one embodiment, the dosage form is suitable for administration in a size 1 or larger capsule.

In another embodiment, provided herein is a dosage form comprising pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 0.5 mg potency of pomalidomide, which is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In some embodiments, the dosage form comprises mannitol and/or starch. In one embodiment where both starch and mannitol are present in the dosage form, starch is present at an amount of about 35 mg, and mannitol is present at an amount that brings the total weight of composition to about 62.5 mg. In some embodiments, the dosage form further comprises sodium stearyl fumarate at an amount of about 0.2 mg or about 0.16 mg. In some embodiments, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceu-

tically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 0.5 mg potency of pomalidomide; about 35 mg pregelatinized starch; about 0.16 mg sodium stearyl fumarate; and spray dried mannitol at an amount that brings the total weight of the dosage form to 62.5 mg; wherein the dosage form is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule.

In another embodiment, provided herein is a dosage form comprising pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 1 mg potency of pomalidomide, which is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In some embodiments, the dosage form comprises mannitol and/or starch. In one embodiment where both starch and mannitol are present in the dosage form, starch is present at an amount of about 70 mg, and mannitol is present at an amount that brings the total weight of composition to about 125 mg. In some embodiments, the dosage farm further comprises sodium stearyl fumarate at an amount of about 0.3 mg or about 0.32 mg. In some embodiments, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 1 mg potency of pomalidomide; about 70 mg pregelatinized starch; about 0.32 mg sodium stearyl fumarate; and spray dried mannitol at an amount that brings the total weight of the dosage form to 125 mg; wherein the dosage form is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In one embodiment, the dosage form is suitable for administration in a size 4 or larger capsule.

In another embodiment, provided herein is a dosage form comprising pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 2 mg potency of pomalidomide, which is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In some embodiments, the dosage form comprises mannitol and/or starch. In one embodiment where both starch and mannitol are present in the dosage form, starch is present at an amount of about 140 mg, and mannitol is present at an amount that brings the total weight of composition to about 250 mg. In some embodiments, the dosage form further comprises sodium stearyl fumarate at an amount of about 0.6 mg or about 0.64 mg. In some embodiments, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 2 mg potency of pomalidomide; about 140 mg pregelatinized starch; about 0.64 mg sodium stearyl fumarate; and spray dried mannitol at an amount that brings the total weight of the dosage form to 250 mg; wherein the dosage form is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In one embodiment, the dosage form is suitable for administration in a size 2 or larger capsule.

In another embodiment, provided herein is a dosage form comprising pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 5 mg potency of pomalidomide, which is stable for a period of at least about 12, about 24, or about 36 months without refrigeration. In some embodiments, the dosage form comprises mannitol and/or starch. In one embodiment where both starch and mannitol are present in the dosage form, starch is present at an amount of about 168 mg, and mannitol is present at an amount that brings the total weight of composition to about 300 mg. In some embodiments, the dosage form further comprises sodium stearyl fumarate at an amount of about 0.8 mg or about 0.75 mg. In some embodiments, provided herein is a dosage form comprising: 1) pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, present at an amount that provides about 5 mg potency of pomalidomide; about 168 mg pregelatinized starch; about 0.75 mg sodium stearyl fumarate; and spray dried mannitol at an amount that brings the total weight of the dosage form to 300 mg; wherein the dosage form is stable for a period of at least 12, about 24, or about 36 months without refrigeration. In one embodiment, the dosage form is suitable for administration in a size 1 or larger capsule.

4.1.1 Second Active Agents

In certain embodiments, provided herein are compositions and dosage form of pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, which may further comprise one or more secondary active ingredients. Certain combinations may work synergistically in the treatment of particular types diseases or disorders, and conditions and symptoms associated with such diseases or disorders. Pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, can also work to alleviate adverse effects associated with certain second active agents, and vice versa.

Specific second active compounds that can be contained in the formulations and dosage forms provided herein vary depending on the specific indication to be treated, prevented or managed.

For instance, for the treatment, prevention or management of cancer, second active agents include, but are not limited to: semaxanib; cyclosporin; etanercept; doxycycline; bortezomib; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran;

paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinzolidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

Other second agents include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; amsacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib (Gleevec®), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene;

translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Yet other second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in multiple myeloma cells (such as, for example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (e.g., PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

In another embodiment, examples of specific second agents according to the indications to be treated, prevented, or managed can be found in the following references, all of which are incorporated herein in their entireties: U.S. Pat. Nos. 6,281,230 and 5,635,517; U.S. publication nos. 2004/0220144, 2004/0190609, 2004/0087546, 2005/0203142, 2004/0091455, 2005/0100529, 2005/0214328, 2005/0239842, 2006/0154880, 2006/0122228, and 2005/0143344; and U.S. provisional application No. 60/631,870.

Examples of second active agents that may be used for the treatment, prevention and/or management of pain include, but are not limited to, conventional therapeutics used to treat or prevent pain such as antidepressants, anticonvulsants, antihypertensives, anxiolytics, calcium channel blockers, muscle relaxants, non-narcotic analgesics, opioid analgesics, anti-inflammatories, cox-2 inhibitors, immunomodulatory agents, alpha-adrenergic receptor agonists or antagonists, immunosuppressive agents, corticosteroids, hyperbaric oxygen, ketamine, other anesthetic agents, NMDA antagonists, and other therapeutics found, for example, in the *Physician's Desk Reference* 2003. Specific examples include, but are not limited to, salicylic acid acetate (Aspirin®), celecoxib (Celebrex®), Enbrel®, ketamine, gabapentin (Neurontin®), phenyloin (Dilantin®), carbamazepine (Tegretol®), oxcarbazepine (Trileptal®), valproic acid (Depakene®), morphine sulfate, hydromorphone, prednisone, griseofulvin, penthonium, alendronate, dyphenhydramide, guanethidine, ketorolac (Acular®), thyrocalcitonin, dimethylsulfoxide (DMSO), clonidine (Catapress®), bretylium, ketanserin, reserpine, droperidol, atropine, phentolamine, bupivacaine, lidocaine, acetaminophen, nortriptyline (Pamelor®), amitriptyline (Elavil®), imipramine (Tofranil®), doxepin (Sinequan®), clomipramine (Anafranil®), fluoxetine (Prozac®) sertraline (Zoloft®), naproxen, nefazodone (Serzone®), venlafaxine (Effexor®), trazodone (Desyrel®), bupropion (Wellbutrin®), mexiletine, nifedipine, propranolol, tramadol, lamotrigine, vioxx, ziconotide, ketamine, dextromethorphan, benzodiazepines, baclofen, tizanidine and phenoxybenzamine.

Examples of second active agents that may be used for the treatment, prevention and/or management of macular degeneration and related syndromes include, but are not limited to, a steroid, a light sensitizer, an integrin, an antioxidant, an interferon, a xanthine derivative, a growth hormone, a neurotrophic factor, a regulator of neovascularization, an anti-VEGF antibody, a prostaglandin, an antibiotic, a phytoestrogen, an anti-inflammatory compound or an antiangiogenesis compound, or a combination thereof. Specific examples include, but are not limited to, verteporfin, purlytin, an angiostatic steroid, rhuFab, interferon-2α, pentoxifylline, tin etiopurpurin, motexafin, lucentis, lutetium, 9-fluoro-11,21-dihydroxy-16,17-1-methylethylidinebis(oxy)pregna-1,4-diene-3,20-dione, latanoprost (see U.S. Pat. No. 6,225,348), tetracycline and its derivatives, rifamycin and its derivatives, macrolides, metronidazole (U.S. Pat. Nos. 6,218,369 and 6,015,803), genistein, genistin, 6'-O-Mal genistin, 6'-O-Ac genistin, daidzein, daidzin, 6'-O-Mal daidzin, daidzin, glycitein, glycitin, 6'-O-Mal glycitin, biochanin A, formononetin (U.S. Pat. No. 6,001,368), triamcinolone acetomide, dexamethasone (U.S. Pat. No. 5,770,589), thalidomide, glutathione (U.S. Pat. No. 5,632,984), basic fibroblast growth factor (bFGF), transforming growth factor b (TGF-b), brain-derived neurotrophic factor (BDNF), plasminogen activator factor type 2 (PAI-2), EYE101 (Eyetech Pharmaceuticals), LY333531 (Eli Lilly), Miravant, and RETISERT implant (Bausch & Lomb). All of the references cited herein are incorporated in their entireties by reference.

Examples of second active agents that may be used for the treatment, prevention and/or management of skin diseases include, but are not limited to, keratolytics, retinoids, α-hydroxy acids, antibiotics, collagen, botulinum toxin, interferon, steroids, and immunomodulatory agents. Specific examples include, but are not limited to, 5-fluorouracil, masoprocol, trichloroacetic acid, salicylic acid, lactic acid, ammonium lactate, urea, tretinoin, isotretinoin, antibiotics, collagen, botulinum toxin, interferon, corticosteroid, transretinoic acid and collagens such as human placental collagen, animal placental collagen, Dermalogen, AlloDerm, Fascia, Cymetra, Autologen, Zyderm, Zyplast, Resoplast, and Isolagen.

Examples of second active agents that may be used for the treatment, prevention and/or management of pulmonary hepertension and related disorders include, but are not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelin antagonists, phosphodiesterase inhibitors (e.g., PDE V inhibitors), endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors, and other therapeutics known to reduce pulmonary artery pressure. Specific examples include, but are not limited to, warfarin (Coumadin®), a diuretic, a cardiac glycoside, digoxin-oxygen, diltiazem, nifedipine, a vasodilator such as prostacyclin (e.g., prostaglandin I2 (PGI2), epoprostenol (EPO, Floran®), treprostinil (Remodulin®), nitric oxide (NO), bosentan (Tracleer®), amlodipine, epoprostenol (Floran®), treprostinil (Remodulin®), prostacyclin, tadalafil (Cialis®), simvastatin (Zocor®), omapatrilat (Vanlev®), irbesartan (Avapro®), pravastatin (Pravachol®), digoxin, L-arginine, iloprost, betaprost, and sildenafil (Viagra®).

Examples of second active agents that may be used for the treatment, prevention and/or management of asbestos-related disorders include, but are not limited to, anthracycline, platinum, alkylating agent, oblimersen (Genasense®), cisplatinum, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, taxotere, irinotecan, capecitabine, cisplatin, thiotepa, fludarabine, car-

boplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, Biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, bleomycin, hyaluronidase, mitomycin C, mepacrine, thiotepa, tetracycline and gemcitabine.

Examples of second active agents that may be used for the treatment, prevention and/or management of parasitic diseases include, but are not limited to, chloroquine, quinine, quinidine, pyrimethamine, sulfadiazine, doxycycline, clindamycin, mefloquine, halofantrine, primaquine, hydroxychloroquine, proguanil, atovaquone, azithromycin, suramin, pentamidine, melarsoprol, nifurtimox, benznidazole, amphotericin B, pentavalent antimony compounds (e.g., sodium stiboglucuronate), interferon gamma, itraconazole, a combination of dead promastigotes and BCG, leucovorin, corticosteroids, sulfonamide, spiramycin, IgG (serology), trimethoprim, and sulfamethoxazole.

Examples of second active agents that may be used for the treatment, prevention and/or management of immunodeficiency disorders include, but are not limited to: antibiotics (therapeutic or prophylactic) such as, but not limited to, ampicillin, tetracycline, penicillin, cephalosporins, streptomycin, kanamycin, and erythromycin; antivirals such as, but not limited to, amantadine, rimantadine, acyclovir, and ribavirin; immunoglobulin; plasma; immunologic enhancing drugs such as, but not limited to, levami sole and isoprinosine; biologics such as, but not limited to, gammaglobulin, transfer factor, interleukins, and interferons; hormones such as, but not limited to, thymic; and other immunologic agents such as, but not limited to, B cell stimulators (e.g., BAFF/BlyS), cytokines (e.g., IL-2, IL-4, and IL-5), growth factors (e.g., TGF-α), antibodies (e.g., anti-CD40 and IgM), oligonucleotides containing unmethylated CpG motifs, and vaccines (e.g., viral and tumor peptide vaccines).

Examples of second active agents that may be used for the treatment, prevention and/or management of CNS disorders include, but are not limited to: opioids; a dopamine agonist or antagonist, such as, but not limited to, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, and Symmetrel; a MAO inhibitor, such as, but not limited to, iproniazid, clorgyline, phenelzine and isocarboxazid; a COMT inhibitor, such as, but not limited to, tolcapone and entacapone; a cholinesterase inhibitor, such as, but not limited to, physostigmine saliclate, physostigmine sulfate, physostigmine bromide, meostigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, and demecarium; an anti-inflammatory agent, such as, but not limited to, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, Rho-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone or betamethasone and other glucocorticoids; and an antiemetic agent, such as, but not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

Examples of second active agents that may be used for the treatment, prevention and/or management of CNS injuries and related syndromes include, but are not limited to, immunomodulatory agents, immunosuppressive agents, antihypertensives, anticonvulsants, fibrinolytic agents, antiplatelet agents, antipsychotics, antidepressants, benzodiazepines, buspirone, amantadine, and other known or conventional agents used in patients with CNS injury/damage and related syndromes. Specific examples include, but are not limited to: steroids (e.g., glucocorticoids, such as, but not limited to, methylprednisolone, dexamethasone and betamethasone); an anti-inflammatory agent, including, but not limited to, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RHo-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone and benzbromarone; a cAMP analog including, but not limited to, db-cAMP; an agent comprising a methylphenidate drug, which comprises 1-threo-methylphenidate, d-threo-methylphenidate, dl-threo-methylphenidate, 1-erythro-methylphenidate, d-erythro-methylphenidate, dl-erythro-methylphenidate, and a mixture thereof; and a diuretic agent such as, but not limited to, mannitol, furosemide, glycerol, and urea.

Examples of second active agent that may be used for the treatment, prevention and/or management of dysfunctional sleep and related syndromes include, but are not limited to, a tricyclic antidepressant agent, a selective serotonin reuptake inhibitor, an antiepileptic agent (gabapentin, pregabalin, carbamazepine, oxcarbazepine, levitiracetam, topiramate), an antiaryhthmic agent, a sodium channel blocking agent, a selective inflammatory mediator inhibitor, an opioid agent, a second immunomodulatory compound, a combination agent, and other known or conventional agents used in sleep therapy. Specific examples include, but are not limited to, Neurontin, oxycontin, morphine, topiramate, amitryptiline, nortryptiline, carbamazepine, Levodopa, L-DOPA, cocaine, α-methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline, fenodolpam mesylate, cabergoline, pramipexole dihydrochloride, ropinorole, amantadine hydrochloride, selegiline hydrochloride, carbidopa, pergolide mesylate, Sinemet CR, Symmetrel, iproniazid, clorgyline, phenelzine, isocarboxazid, tolcapone, entacapone, physostigmine saliclate, physostigmine sulfate, physostigmine bromide, meo-

stigmine bromide, neostigmine methylsulfate, ambenonim chloride, edrophonium chloride, tacrine, pralidoxime chloride, obidoxime chloride, trimedoxime bromide, diacetyl monoxim, endrophonium, pyridostigmine, demecarium, naproxen sodium, diclofenac sodium, diclofenac potassium, celecoxib, sulindac, oxaprozin, diflunisal, etodolac, meloxicam, ibuprofen, ketoprofen, nabumetone, refecoxib, methotrexate, leflunomide, sulfasalazine, gold salts, RHo-D Immune Globulin, mycophenylate mofetil, cyclosporine, azathioprine, tacrolimus, basiliximab, daclizumab, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone, zileuton, aurothioglucose, gold sodium thiomalate, auranofin, methotrexate, colchicine, allopurinol, probenecid, sulfinpyrazone, benzbromarone, betamethasone and other glucocorticoids, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and a mixture thereof.

Examples of second active agents that may be used for the treatment, prevention and/or management of hemoglobinopathy and related disorders include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; and G-CSF; hydroxyurea; butyrates or butyrate derivatives; nitrous oxide; hydroxy urea; HEMOXIN™ (NIPRISAN™; see U.S. Pat. No. 5,800,819); Gardos channel antagonists such as clotrimazole and triaryl methane derivatives; Deferoxamine; protein C; and transfusions of blood, or of a blood substitute such as Hemospan™ or Hemospan™ PS (Sangart).

4.2. Process for Making Dosage Forms

Dosage forms provided herein can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the excipient, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly admixing (e.g., direct blend) the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if necessary, shaping the product into the desired presentation (e.g., compaction such as roller-compaction). If desired, tablets can be coated by standard aqueous or non-aqueous techniques.

A dosage form provided herein can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient as above and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Encapsulation of the dosage forms provided herein can be done using capsules of methylcellulose, calcium alginate, or gelatin.

In some embodiments, the active ingredients and excipients are directly blended and loaded into, for example, a capsule, or compressed directly into tablets. A direct-blended dosage form may be more advantageous than a compacted (e.g., roller-compacted) dosage form in certain instances, since direct-blending can reduce or eliminate the harmful health effects that may be caused by airborne particles of ingredients during the manufacture using compaction process.

Direct blend formulations may be advantageous in certain instances because they require only one blending step, that of the active and excipients, before being processed into the final dosage form, e.g., tablet or capsule. This can reduce the production of airborne particle or dust to a minimum, while roller-compaction processes may be prone to produce dust. In roller-compaction process, the compacted material is often milled into smaller particles for further processing. The milling operation can produce significant amounts of airborne particles, since the purpose for this step in manufacturing is to reduce the materials particle size. The milled material is then blended with other ingredients prior to manufacturing the final dosage form.

For certain active ingredients, in particular for a compound with a low solubility, the active ingredient's particle size is reduced to a fine powder in order to help increase the active ingredient's rate of solubilization. The increase in the rate of solubilization is often necessary for the active ingredient to be effectively absorbed in the gastrointestinal tract. However for fine powders to be directly-blended and loaded onto capsules, the excipients should preferably provide certain characteristics which render the ingredients suitable for the direct-blend process. Examples of such characteristics include, but are not limited to, acceptable flow characteristics. In one embodiment, therefore, provided herein is the use of, and compositions comprising, excipients which may provide characteristics, which render the resulting mixture suitable for direct-blend process, e.g., good flow characteristics.

4.2.1. Screening

The process for making the pharmaceutical compositions of the invention preferably includes the screening of the active ingredient and the excipient(s). In one embodiment, the active ingredient is passed through a screen having openings of about 200 microns to about 750 microns. In another embodiment, the active ingredient is passed through a screen with openings of about 200 microns to about 400 microns. In one embodiment, the active ingredient is passed through a screen having openings of about 300 to about 400 microns. Depending on the excipient(s) used, the screen openings vary. For example, disintegrants and binders are passed through openings of about 430 microns to about 750 microns, from about 600 microns to about 720 microns, or about 710 microns. Lubricants are typically passed through smaller openings, e.g., about 150 microns to about 250 microns screen. In one embodiment, the lubricant is passed through a screen opening of about 210 microns.

4.2.2. Pre-Blending

After the ingredients are screened, the excipient and active ingredient are mixed in a diffusion mixer. In one embodiment, the mixing time is from about 1 minute to about 50 minutes, from about 5 minutes to about 45 minutes, from about 10 minutes to about 40 minutes, or from about 10 minutes to about 25 minutes. In another embodiment, the mixing time is about 15 minutes.

When more than one excipients are used, the excipients may be admixed in a tumble blender for about 1 minute to about 20 minutes, or for about 5 minutes to about 10 minutes, prior to mixing with the active ingredient.

4.2.3. Roller Compaction

In one embodiment, the pre-blend may optionally be passed through a roller compactor with a hammer mill attached at the discharge of the compactor.

4.2.4. Final Blend

When a lubricant, e.g., sodium stearyl fumarate, is used, the lubricant is mixed with the pre-blend at the end of the process to complete the pharmaceutical composition. This additional mixing is from about 1 minute to about 10 minutes, or from about 3 minutes to about 5 minutes.

4.2.5. Encapsulation

The formulation mixture is then encapsulated into the desired size capsule shell using, for example, a capsule filling machine or a rotary tablet press.

4.3. Kits

Pharmaceutical packs or kits which comprise pharmaceutical compositions or dosage forms provided herein are also provided. An example of a kit comprises notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

4.4. Methods of Treatment, Prevention, and Management

Provided herein are methods of treating, preventing, and/or managing certain diseases or disorders using the formulations, compositions, or dosage forms provided herein.

Examples of diseases or disorders include, but are not limited to, cancer, disorders associated with angiogenesis, pain including, but not limited to, Complex Regional Pain Syndrome ("CRPS"), Macular Degeneration ("MD") and related syndromes, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases, immunodeficiency disorders, CNS disorders, CNS injury, atherosclerosis and related disorders, dysfunctional sleep and related disorders, hemoglobinopathy and related disorders (e.g., anemia), INFα related disorders, and other various diseases and disorders.

Examples of cancer and precancerous conditions include, but are not limited to, those described in U.S. Pat. Nos. 6,281,230 and 5,635,517 to Muller et al., in various U.S. patent publications to Zeldis, including publication nos. 2004/0220144A1, published Nov. 4, 2004 (Treatment of Myelodysplastic Syndrome); 2004/0029832A1, published Feb. 12, 2004 (Treatment of Various Types of Cancer); and 2004/0087546, published May 6, 2004 (Treatment of Myeloproliferative Diseases). Examples also include those described in WO 2004/103274, published Dec. 2, 2004. All of these references are incorporated herein in their entireties by reference.

Certain examples of cancer include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are also useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias. The compounds provided herein can be used for treating, preventing or managing either primary or metastatic tumors.

Other cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma (localized melanoma, including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation.

In one embodiment, the diseases or disorders are various forms of leukemias such as chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia, including leukemias that are relapsed, refractory or resistant, as disclosed in U.S. publication no. 2006/0030594, published Feb. 9, 2006, which is incorporated in its entirety by reference.

The term "leukemia" refers malignant neoplasms of the blood-forming tissues. The leukemia includes, but is not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia. The leukemia can be relapsed, refractory or resistant to conventional therapy. The term "relapsed" refers to a situation where patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. The term "refractory or resistant" refers to a circumstance where patients, even after intensive treatment, have residual leukemia cells in their marrow.

In another embodiment, the diseases or disorders are various types of lymphomas, including Non-Hodgkin's lymphoma (NHL). The term "lymphoma" refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. "NHL" refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal tract. Examples of NHL include, but are not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma, diffuse small-cleaved cell lymphoma (DSCCL), follicular lym-

phoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, arthritis, endometriosis. Crohn's disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, and 5q-deletion syndrome.

Examples of pain include, but are not limited to those described in U.S. patent publication no. 2005/0203142, published Sep. 15, 2005, which is incorporated herein by reference. Specific types of pain include, but are not limited to, nociceptive pain, neuropathic pain, mixed pain of nociceptive and neuropathic pain, visceral pain, migraine, headache and post-operative pain.

Examples of nociceptive pain include, but are not limited to, pain associated with chemical or thermal burns, cuts of the skin, contusions of the skin, osteoarthritis, rheumatoid arthritis, tendonitis, and myofascial pain.

Examples of neuropathic pain include, but are not limited to, CRPS type I, CRPS type II, reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, reflex dystrophy, sympathetically maintained pain syndrome, causalgia, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, trigeminal neuralgia, post herpetic neuralgia, cancer related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, spinal cord injury pain, central post-stroke pain, radiculopathy, diabetic neuropathy, post-stroke pain, luetic neuropathy, and other painful neuropathic conditions such as those induced by drugs such as vincristine and velcade.

As used herein, the terms "complex regional pain syndrome," "CRPS" and "CRPS and related syndromes" mean a chronic pain disorder characterized by one or more of the following: pain, whether spontaneous or evoked, including allodynia (painful response to a stimulus that is not usually painful) and hyperalgesia (exaggerated response to a stimulus that is usually only mildly painful); pain that is disproportionate to the inciting event (e.g., years of severe pain after an ankle sprain); regional pain that is not limited to a single peripheral nerve distribution; and autonomic dysregulation (e.g., edema, alteration in blood flow and hyperhidrosis) associated with trophic skin changes (hair and nail growth abnormalities and cutaneous ulceration).

Examples of MD and related syndromes include, but are not limited to, those described in U.S. patent publication no. 2004/0091455, published May 13, 2004, which is incorporated herein by reference. Specific examples include, but are not limited to, atrophic (dry) MD, exudative (wet) MD, age-related maculopathy (ARM), choroidal neovascularisation (CNVM), retinal pigment epithelium detachment (PED), and atrophy of retinal pigment epithelium (RPE).

Examples of skin diseases include, but are not limited to, those described in U.S. publication no. 2005/0214328A1, published Sep. 29, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to keratoses and related symptoms, skin diseases or disorders characterized with overgrowths of the epidermis, acne, and wrinkles.

As used herein, the term "keratosis" refers to any lesion on the epidermis marked by the presence of circumscribed overgrowths of the horny layer, including but not limited to actinic keratosis, seborrheic keratosis, keratoacanthoma, keratosis follicularis (Darier disease), inverted follicular keratosis, palmoplantar keratoderma (PPK, keratosis palmaris et plantaris), keratosis pilaris, and stucco keratosis. The term "actinic keratosis" also refers to senile keratosis, keratosis senilis, verruca senilis, plana senilis, solar keratosis, keratoderma or keratoma. The term "seborrheic keratosis" also refers to seborrheic wart, senile wart, or basal cell papilloma. Keratosis is characterized by one or more of the following symptoms: rough appearing, scaly, erythematous papules, plaques, spicules or nodules on exposed surfaces (e.g., face, hands, ears, neck, legs and thorax), excrescences of keratin referred to as cutaneous horns, hyperkeratosis, telangiectasias, elastosis, pigmented lentigines, acanthosis, parakeratosis, dyskeratoses, papillomatosis, hyperpigmentation of the basal cells, cellular atypia, mitotic figures, abnormal cell-cell adhesion, dense inflammatory infiltrates and small prevalence of squamous cell carcinomas.

Examples of skin diseases or disorders characterized with overgrowths of the epidermis include, but are not limited to, any conditions, diseases or disorders marked by the presence of overgrowths of the epidermis, including but not limited to, infections associated with papilloma virus, arsenical keratoses, sign of Leser-Trélat, warty dyskeratoma (WD), trichostasis spinulosa (TS), erythrokeratodermia variabilis (EKV), ichthyosis fetalis (harlequin ichthyosis), knuckle pads, cutaneous melanoacanthoma, porokeratosis, psoriasis, squamous cell carcinoma, confluent and reticulated papillomatosis (CRP), acrochordons, cutaneous horn, cowden disease (multiple hamartoma syndrome), dermatosis papulosa nigra (DPN), epidermal nevus syndrome (ENS), ichthyosis vulgaris, molluscum contagiosum, prurigo nodularis, and acanthosis nigricans (AN).

Examples of pulmonary disorders include, but are not limited to, those described in U.S. publication no. 2005/0239842A1, published Oct. 27, 2005, which is incorporated herein by reference. Specific examples include pulmonary hypertension and related disorders. Examples of pulmonary hypertension and related disorders include, but are not limited to: primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vascular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus including systemic and cutaneous lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

Examples of asbestos-related disorders include, but not limited to, those described in U.S. publication no. 2005/0100529, published May 12, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, mesothelioma, asbestosis, malignant pleural effusion, benign exudative effusion, pleural plaques, pleural calcification, diffuse pleural thickening, rounded atelectasis, fibrotic masses, and lung cancer.

Examples of parasitic diseases include, but are not limited to, those described in U.S. publication no. 2006/0154880, published Jul. 13, 2006, which is incorporated herein by reference. Parasitic diseases include diseases and disorders caused by human intracellular parasites such as, but not limited to, *P. falcifarium, P. ovale, P. vivax, P. malariae, L. donovari, L. infantum, L. aethiopica, L. major, L. tropica, L. mexicana, L. braziliensis, T. Gondii, B. microti, B. divergens, B. coli, C. parvum, C. cayetanensis, E. histolytica, Z belli, S. mansonii, S. haematobium, Trypanosoma* ssp., *Toxoplasma* ssp., and *O. volvulus*. Other diseases and disorders caused by non-human intracellular parasites such as, but not limited to, *Babesia bovis, Babesia canis, Banesia Gibsoni, Besnoitia darlingi, Cytauxzoon felis, Eimeria* ssp., *Hammondia* ssp., and *Theileria* ssp., are also encompassed. Specific examples include, but are not limited to, malaria, babesiosis, trypanosomiasis, leishmaniasis, toxoplasmosis, meningoencephalitis, keratitis, amebiasis, giardiasis, cryptosporidiosis, isosporiasis, cyclosporiasis, microsporidiosis, *ascariasis*, trichuriasis, ancylostomiasis, strongyloidiasis, toxocariasis, trichinosis, lymphatic filariasis, onchocerciasis, filariasis, schistosomiasis, and dermatitis caused by animal schistosomes.

Examples of immunodeficiency disorders include, but are not limited to, those described in U.S. application Ser. No. 11/289,723, filed Nov. 30, 2005. Specific examples include, but not limited to, adenosine deaminase deficiency, antibody deficiency with normal or elevated Igs, ataxia-tenlangiectasia, bare lymphocyte syndrome, common variable immunodeficiency, Ig deficiency with hyper-IgM, Ig heavy chain deletions, IgA deficiency, immunodeficiency with thymoma, reticular dysgenesis, Nezelof syndrome, selective IgG subclass deficiency, transient hypogammaglobulinemia of infancy, Wistcott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency.

Examples of CNS disorders include, but are not limited to, those described in U.S. publication no. 2005/0143344, published Jun. 30, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, include, but are not limited to, Amyotrophic Lateral Sclerosis, Alzheimer Disease, Parkinson Disease, Huntington's Disease, Multiple Sclerosis other neuroimmunological disorders such as Tourette Syndrome, delerium, or disturbances in consciousness that occur over a short period of time, and amnestic disorder, or discreet memory impairments that occur in the absence of other central nervous system impairments.

Examples of CNS injuries and related syndromes include, but are not limited to, those described in U.S. publication no. 2006/0122228, published Jun. 8, 2006, which is incorporated herein by reference. Specific examples include, but are not limited to, CNS injury/damage and related syndromes, include, but are not limited to, primary brain injury, secondary brain injury, traumatic brain injury, focal brain injury, diffuse axonal injury, head injury, concussion, post-concussion syndrome, cerebral contusion and laceration, subdural hematoma, epidermal hematoma, post-traumatic epilepsy, chronic vegetative state, complete SCI, incomplete SCI, acute SCI, subacute SCI, chronic SCI, central cord syndrome, Brown-Sequard syndrome, anterior cord syndrome, conus medullaris syndrome, cauda equina syndrome, neurogenic shock, spinal shock, altered level of consciousness, headache, nausea, emesis, memory loss, dizziness, diplopia, blurred vision, emotional lability, sleep disturbances, irritability, inability to concentrate, nervousness, behavioral impairment, cognitive deficit, and seizure.

Other disease or disorders include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythrematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

Examples of atherosclerosis and related conditions include, but are not limited to, those disclosed in U.S. publication no. 2002/0054899, published May 9, 2002, which is incorporated herein by reference. Specific examples include, but are not limited to, all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting. All forms of vascular intervention are contemplated herein, including diseases of the cardiovascular and renal system, such as, but not limited to, renal angioplasty, percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), carotid percutaneous transluminal angioplasty (PTA), coronary by-pass grafting, angioplasty with stent implantation, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries, and surgical intervention using impregnated artificial grafts. The following chart provides a listing of the major systemic arteries that may be in need of treatment, all of which are contemplated herein:

Artery	Body Areas Supplied
Axillary	Shoulder and axilla
Brachial	Upper arm
Brachiocephalic	Head, neck, and arm
Celiac	Divides into left gastric, splenic, and hepatic arteries
Common carotid	Neck
Common iliac	Divides into external and internal iliac arteries
Coronary	Heart
Deep femoral	Thigh
Digital	Fingers
Dorsalis pedis	Foot
External carotid	Neck and external head regions
External iliac	Femoral artery
Femoral	Thigh
Gastric	Stomach
Hepatic	Liver, gallbladder, pancreas, and duodenum
Inferior mesenteric	Descending colon, rectum, and pelvic wall
Internal carotid	Neck and internal head regions
Internal iliac	Rectum, urinary bladder, external genitalia, buttocks muscles, uterus and vagina
Left gastric	Esophagus and stomach
Middle sacral	Sacrum
Ovarian	Ovaries
Palmar arch	Hand
Peroneal	Calf
Popliteal	Knee
Posterior tibial	Calf
Pulmonary	Lungs
Radial	Forearm
Renal	Kidney
Splenic	Stomach, pancreas, and spleen

-continued

Artery	Body Areas Supplied
Subclavian	Shoulder
Superior mesenteric	Pancreas, small intestine, ascending and transverse colon
Testicular	Testes
Ulnar	Forearm

Examples of dysfunctional sleep and related syndromes include, but are not limited to, those disclosed in U.S. publication no. 2005/0222209A1, published Oct. 6, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking sleep eating, and dysfunctional sleep associated with chronic neurological or inflammatory conditions. Chronic neurological or inflammatory conditions, include, but are not limited to, Complex Regional Pain Syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's Disease, bradykinesia; muscle rigidity; parkinsonian tremor; parkinsonian gait; motion freezing; depression; defective long-term memory, Rubinstein-Taybi syndrome (RTS); dementia; postural instability; hypokinetic disorders; synuclein disorders; multiple system atrophies; striatonigral degeneration; olivopontocerebellar atrophy; Shy-Drager syndrome; motor neuron disease with parkinsonian features; Lewy body dementia; Tau pathology disorders; progressive supranuclear palsy; corticobasal degeneration; frontotemporal dementia; amyloid pathology disorders; mild cognitive impairment; Alzheimer disease with parkinsonism; Wilson disease; Hallervorden-Spatz disease; Chediak-Hagashi disease; SCA-3 spinocerebellar ataxia; X-linked dystonia parkinsonism; prion disease; hyperkinetic disorders; chorea; ballismus; dystonia tremors; Amyotrophic Lateral Sclerosis (ALS); CNS trauma and myoclonus.

Examples of hemoglobinopathy and related disorders include, but are not limited to, those described in U.S. publication no. 2005/0143420A1, published Jun. 30, 2005, which is incorporated herein by reference. Specific examples include, but are not limited to, hemoglobinopathy, sickle cell anemia, and any other disorders related to the differentiation of CD34+ cells.

Examples of TNFα related disorders include, but are not limited to, those described in WO 98/03502 and WO 98/54170, both of which are incorporated herein in their entireties by reference. Specific examples include, but are not limited to: endotoxemia or toxic shock syndrome; cachexia; adult respiratory distress syndrome; bone resorption diseases such as arthritis; hypercalcemia; Graft versus Host Reaction; cerebral malaria; inflammation; tumor growth; chronic pulmonary inflammatory diseases; reperfusion injury; myocardial infarction; stroke; circulatory shock; rheumatoid arthritis; Crohn's disease; HIV infection and AIDS; other disorders such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis and other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythromatosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS; disorders such as septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, radiation damages, and hyperoxic alveolar injury; viral infections, such as those caused by the herpes viruses; viral conjunctivitis; or atopic dermatitis.

In other embodiments, the use of formulations, compositions or dosage forms provided herein in various immunological applications, in particular, as vaccine adjuvants, particularly anticancer vaccine adjuvants, as disclosed in U.S. Publication No. 2007/0048327, published Mar. 1, 2007, which is incorporated herein in its entirety by reference, is also encompassed. These embodiments also relate to the uses of the compositions, formulations, or dosage forms provided herein in combination with vaccines to treat or prevent cancer or infectious diseases, and other various uses such as reduction or desensitization of allergic reactions.

5. EXAMPLES

Embodiments provided herein may be more fully understood by reference to the following examples. These examples are meant to be illustrative of pharmaceutical compositions and dosage forms provided herein, but are not in any way limiting.

5.1 Example 1

0.5 mg Strength Pomalidomide Dosage Capsule

Table 1 illustrates a batch formulation and single dosage formulation for a 0.5 mg strength pomalidomide single dose unit in a size #4 capsule.

TABLE 1

Formulation for 0.5 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~1%	0.5*
Starch 1500	56%	35
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.16
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	62.5

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 0.5 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #4 capsule.

5.2 Example 2

1 mg Strength Pomalidomide Dosage Capsule

Table 2 illustrates a batch formulation and single dosage formulation for a 1 mg strength pomalidomide single dose unit in a size #4 capsule.

TABLE 2

Formulation for 1 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~1%	1*
Starch 1500	56%	70
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.32
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	125

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 1 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #4 capsule.

5.3 Example 3

2 mg Strength Pomalidomide Dosage Capsule

Table 3 illustrates a batch formulation and single dosage formulation for a 2 mg pomalidomide single dose unit in a size #2 capsule.

TABLE 3

Formulation for 2 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~1%	2*
Starch 1500	56%	140
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.64
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	250

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 2 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #2 capsule.

5.4 Example 4

3 mg Strength Pomalidomide Dosage Capsule

Table 4 illustrates a batch formulation and single dosage formulation for a 0.5 mg strength pomalidomide single dose unit in a size #2 capsule.

TABLE 4

Formulation for 3 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~1.6%	3*
Starch 1500	56%	100.8
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.45
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	180

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 3 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #2 capsule.

5.5 Example 5

4 mg Strength Pomalidomide Dosage Capsule

Table 5 illustrates a batch formulation and single dosage formulation for a 0.5 mg strength pomalidomide single dose unit in a size #2 capsule.

TABLE 5

Formulation for 4 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~1.6%	4*
Starch 1500	56%	134.4
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.6
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	240

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 4 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #2 capsule.

5.6 Example 6

5 mg Strength Pomalidomide Dosage Capsule

Table 6 illustrates a batch formulation and single dosage formulation for a 5 mg pomalidomide single dose unit in a size #1 capsule.

TABLE 4

Formulation for 5 mg strength pomolidomide capsule

Material	Percent By Weight	Quantity (mg/capsule)
Pomolidomide	~2%	5*
Starch 1500	56%	168
Sodium Stearyl Fumarate (PRUV)	~0.3%	0.75
Spray Dried Mannitol (Mannogem EZ)	remainder	remainder
Total	100.0%	300

*Denotes amount of pomolidomide that corresponds to the amount that provides the potency of 5 mg of pomolidomide.

Pomalidomide was passed through a 35-mesh screen. Mannitol and starch were each separately passed through a 25-mesh screen. Pomalidomide was pre-blended with a portion of mannitol and starch. The pre-blend was milled through a 0.039 inch screen. The remainder of the mannitol and starch was also milled through a 0.039 inch screen. The pre-blend was blended with the reminder of mannitol and starch. To this blend, sodium fumarate, which was passed through a 60 mesh screen, was further blended. The final blend was encapsulated into a size #1 capsule.

5.7 Example 7

Stability of Formulation

Accelerated stability was assessed under 40° C./75% RH, and levels of impurities over the time period of initial, 1 month, 3 months, and 6 months were determined. Long term stability under 25° C./60% RH is also assessed during 0-24 months. For determination of the level of Impurities, an HPLC gradient method was employed using the following conditions:

Column:	Zorbax SB-CN, 150 mm × 4.6 mm id, 5 μm particle size		
Temperature:	Ambient		
Mobile Phase:	A: 10/90 methanol/0.1% trifluoroacetic acid B: 80/20 methanol/0.1% trifluoroacetic acid		
Gradient Profile:	Time (min)	% A	% B
	0	90	10
	5	90	10
	50	20	80
	51	90	10
	60	90	10
Flow Rate:	1.0 mL/min		
Injection Volume:	25 μL		
Detection:	UV, 240 nm		
Run Time:	60 minutes.		

From the experiments, it was observed that the impurities in the formulation provided herein stayed negligent throughout the time period investigated. The performance characteristics of the dosage also maintained throughout the time period investigated. These results show that the formulations provided herein have adequate stability for clinical and other uses.

While examples of certain particular embodiments are provided herein, it will be apparent to those skilled in the art that various changes and modifications may be made. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. An oral dosage form in the form of a capsule which weighs 62.5 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 0.5 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

2. The dosage form of claim **1**, which is to be administered in the form of a size 4 or larger capsule.

3. An oral dosage form in the form of a capsule which weighs 125 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

4. The dosage form of claim **3**, which is to be administered in the form of a size 4 or larger capsule.

5. An oral dosage form in the form of a capsule which weighs 250 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 2 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

6. The dosage form of claim **5**, which is to be administered in the form of a size 2 or larger capsule.

7. An oral dosage form in the form of a capsule which weighs 180 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 3 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

8. The dosage form of claim **7**, which is to be administered in the form of a size 2 or larger capsule.

9. An oral dosage form in the form of a capsule which weighs 240 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 4 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

10. The dosage form of claim **9**, which is to be administered in the form of a size 2 or larger capsule.

11. An oral dosage form in the form of a capsule which weighs 300 mg and comprises: 1) pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 5 mg of 100% pure pomalidomide; 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

12. The dosage form of claim **11**, which is to be administered in the form of a size 1 or larger capsule.

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Exhibit 9

Exhibit 10